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INTERRELATIONS IN THE STREPTOCOCCUS GROUP WITH SPECIAL REFERENCE TO ANAPHY- LACTIC REACTIONS.*

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Numerous methods for the differentiation of streptococci have been attempted by many workers with varying degrees of success. Various morphological and cultural details were used, especially by the earlier workers in this field. On the whole specific immune sera have not been satisfactory on account of the fact that this group is not highly sensitive to the various immune reactions. The acid agglutination method, used by Michaelis with success in connection with the typhoid-colon group, has recently been applied by Bergey¹ to the streptococcus group without definite results. Fermentation tests are undoubtedly of value, but on account of the tendency of the organisms to vary in their fermentative powers this method is not an absolutely reliable one for differential purposes.

The clinical manifestations of streptococcus infections are so varied that the idea that important differences must exist between the cocci constantly appeals to one. I became especially interested in this problem when studying the flora of the tonsillar crypts in cases of chronic renal, cardiac, and articular diseases. Though there was good reason to believe that the clinical condition was caused by the tonsillar infections in many instances, still the streptococci isolated from the various cases could not be differentiated.² Erysipelas, puerperal sepsis, septicemia, pyemia, various skin lesions, tonsillitis, etc., are only further illustrations of this point.

In the study of these organisms, it is undoubtedly true that emphasis has usually been placed on minute and often unimportant details which might serve to differentiate them, rather than on points which might serve to demonstrate their close relationship or, possibly their identity. Reference may here be made to my brief preliminary communication entitled "Relation of Varieties of

* Received for publication March 5, 1913.

¹ *Jour. Med. Res.*, 1911, 27, p. 67.

² *Jour. Infect. Dis.*, 1912, 10, p. 148.

Streptococci with Especial Reference to Experimental Arthritis,"¹ which may serve as an introduction to the present paper.

The relations existing between members of the streptococcus group were there represented in a table which has since been amplified but not essentially altered by the addition of other data. This amplified table is published now together with some explanatory notes and also with some data bearing upon the possible transformation of one variety into another. In order to inquire farther into the relations of members of this group of organisms some interanaphylactic experiments have been made with streptococci from various sources the details of which follow.

In Table 1, the organisms have been arranged in order as determined by morphological, cultural, and experimental data. These are: (1) hemolysis on blood agar plates, (2) production of green colonies on blood agar plates, (3) capsule formation, (4) solubility in bile, (5) inulin fermentation, (6) experimental arthritis in rabbits, and (7) experimental endocarditis in rabbits. When the members of the streptopneumococcus group are arranged in the order given in the table, it will be seen that a more or less gradual transition occurs from one variety to another with reference to the properties enumerated. In general, the sign \pm indicates that the particular property in question may occur rarely or to a very slight degree and the number of + signs is intended to give a general idea of the intensity or the relative frequency, as the case may be, of the property.

TABLE 1.
RELATIONS OF STREPTOCOCCI.

	Organisms	Hemolysis	Green Colonies on Blood Agar	Capsule	Solubility in Bile	Inulin Fermentation	Experimental Arthritis	Experimental Endocarditis
1	Str. hemolyticus.....	+++	o	+	o	o	+++	\pm
2	Str. epidemicus.....	++	o	+	\pm	+	+++	+
3	Str. mucosus.....	\pm	++	+++	+++	++	++	\pm
4	Str. pneumoniae.....	o	+++	+	++	++	\pm	+?.
5	Str. viridans.....	o	+++	o	o	+	\pm	+++

The first member or group in the series, *Streptococcus hemolyticus*, is the common streptococcus usually called *Streptococcus pyogenes*. Here are included the streptococci found in acute sore throats,

¹ Jour. Am. Med. Assn., 1912, 58, p. 1283.

septicemias, etc.; also the streptococci that commonly occur about the tonsils and throat in cases of arthritis, nephritis, etc. It should be stated that the term *Streptococcus pyogenes*, as commonly used, is a broad one and may perhaps with equal propriety be applied to the first three members of the series. No. 2 is the organism that was encountered in the epidemic of sore throat that prevailed in Chicago during the winter season of 1911-12. For convenience we refer to this organism as the epidemic streptococcus. No. 3 is the fairly well-defined organism, now commonly called *Streptococcus mucosus*, which was formerly known as *Streptococcus mucosus capsulatus*. *Streptococcus capsulatus* and *Pneumococcus mucosus* are other terms which have been applied to this organism. No. 4 in the series is the ordinary pneumococcus which for the sake of uniformity of nomenclature is referred to as *Streptococcus pneumoniae*, a term not infrequently used by authorities in connection with this germ. No. 5 is *Streptococcus viridans*, an organism to which especial attention was first called by Schottmüller and Rosenow. This organism is commonly found about the mouth and throat, and appears to be identical with the organism found in subacute or chronic infectious endocarditis as observed by Rosenow, Schottmüller, Libman, and others.

These organisms all appear to be fairly well defined and, as stated, arrange themselves in definite order in the table with respect to certain properties. As regards hemolysis, the first members are hemolytic; as we descend the series, this property vanishes. The production of green colonies on blood is not noted in the first members but occurs lower in the series.

Capsule formation is most marked in the middle member, namely *Streptococcus mucosus*, and diminishes in either direction, the members at the top and bottom of the series ordinarily not showing this property. Exceptions to this rule occur especially in the hemolytic streptococcus group, when capsules may appear as a result of growth in animals or animal fluids. The question then arises as to their possible transformation into the second or epidemic type.

In 1900 Neufeld[†] first called attention to the relative solubility

[†] *Ztschr. f. Hyg. u. Infektionskrankh.*, 1900, 34, p. 454.

in bile of this group of organisms, and his results have since been confirmed especially by Grixoni¹ and by Libman.² As a means of differentiating streptococci and pneumococci, Libman and Cellar³ have called particular attention to this method. The results of various investigators including some data obtained by the writer on this point, indicate, as shown in the table, that practically all strains of *Streptococcus hemolyticus* are insoluble in rabbit's bile. *Streptococcus epidemicus* is insoluble, or only to a very slight extent soluble, in rabbit's bile. *Streptococcus mucosus* is highly soluble, and the pneumococcus is also soluble, but somewhat less so than *Streptococcus mucosus*. *Streptococcus viridans* or endocarditic coccus is insoluble. It will thus be seen that in a general way the solubility in bile runs parallel with capsule formation. Whether or not it is dependent upon capsule formation has not been definitely determined.

Sugar fermentation with the streptococcus group has on the whole not been trustworthy or satisfactory on account of inconsistency of results. The work of Walker⁴ in this respect may be consulted. The fermentation of inulin has been used as a differential point between pneumococci and streptococci and is of value, though it cannot be considered entirely reliable. For example, Libman found that of 19 strains of pneumococci, all fermented inulin except two; of 12 strains of *Streptococcus mucosus*, all fermented inulin, and of 69 streptococci, all failed to ferment inulin except two and these lost this property after animal passage. Of *Streptococcus viridans* from cases of endocarditis, about one third ferment inulin. On account of the variation of this property the relative fermentative power of the various cocci can only be represented roughly in the table.

In a study of the pathogenic properties of various streptococci, I have found that experimental arthritis is readily produced in rabbits by the upper three varieties when the organisms are given intravenously.⁵ It is rarely produced by strains of the last two organisms. In general the reverse is true concerning experimental

¹ Riv. crit. di clin. Med., 1909, 10, 17.

² Proc. Path. Soc., New York, 1908, 8, p. 40.

³ Am. Jour. Med. Sc., 1910, 140, p. 516.

⁴ Proc. Royal Soc. London, 1911, Series B, 83, p. 541.

⁵ Jour. Am. Med. Assn., 1912, 58, p. 1852.

endocarditis in rabbits. In about 10 per cent of rabbits inoculated intravenously with hemolytic and epidemic streptococci, endocarditis results. Rosenow¹ has shown that experimental endocarditis may be produced in nearly every instance by inoculation with organisms of the viridans type.

It is to be noted that the transition from one organism to another is more or less gradual, a point which brings up the question of the possible transformation of one variety into another. The variability of bacteria is a subject which has been studied by many observers for years and many data concerning numerous varieties exist. For example, the transformation of a golden staphylococcus into the white variety is a well-known phenomenon. The loss of the property of hemolysis by strains of *B. coli* has been repeatedly observed. Ruediger² and also Anthony³ have noted the occasional loss of hemolysis in certain strains of streptococci. The latter writer noted changes in hemolysing power in about five per cent of the organisms tested. Attention has already been called⁴ to the transition of the epidemic streptococcus to the ordinary hemolytic streptococcus and vice versa. The strains vary markedly in this respect, some apparently retaining their properties with much greater tenacity than others.

That more extensive variations also take place at times and under certain conditions is undoubtedly true. I presume it is a fact that nearly every investigator working in bacteriology, especially with minute cultural details, can cite observations which at least suggest mutation.⁵ A few instances which have come under my observation are here cited. Five guinea-pigs were each inoculated with one cubic centimeter of a 24-hour broth culture of a typical hemolytic streptococcus (No. 243), which several weeks previously had been isolated from the tonsils of a case of ordinary sore throat. The zone of hemolysis was wide and clear and without green color. There was no capsule and the growth on blood agar slants was not moist or spreading. Four of the guinea-pigs showed

¹ *Jour. Infect. Dis.*, 1909, 6, p. 245.

² *Jour. Infect. Dis.*, 1906, 3, p. 663.

³ *Ibid.*, 1909, 6, p. 332.

⁴ *Jour. Am. Med. Assn.*, 1912, 58, p. 1852; also Rosenow, *Jour. Infect. Dis.*, 1912, 11, p. 338.

⁵ An excellent monograph including literature on this subject is by Hans Pringsheim: *Die Variabilität niederer Organismen*, Berlin, 1910.

little or no reaction and were alive and well at the end of three weeks. One of the animals died on the 10th day after the infection. A gelatinous turbid exudate was found in the peritoneum and in the pleural cavities. Smears of the exudate revealed many encapsulated diplococci and short chains. Cultures from the heart's blood and the exudates gave pure growths of an organism that has the properties of *Streptococcus mucosus*. The growth on blood agar is very moist, raised, and mucoid. The colonies are distinctly green and about them is a green zone without hemolysis or with only a slight trace appearing after two or three days. The organism grows scarcely at all on plain media or on sugar media. It is distinctly soluble in rabbit's bile but does not ferment inulin. At the present time, which is about one month after isolation, there is no tendency to revert to the hemolytic type. The growth is perhaps less viscid and spreading than when first isolated, but on blood plates the colonies are distinctly green and perhaps tend to resemble the pneumococcus more than the hemolytic or epidemic streptococci. It is highly virulent for animals and animal passage causes an increase in its mucoid properties. While the tendency culturally seems to be toward the pneumococcus type, morphologically it is not a pneumococcus. It should be stated that the original streptococcus, which in the first place was grown from a single plate colony, was plated later without finding any colonies of the mucosus type. It appeared to be in the original, therefore a pure strain.

Another instance of a transformation in the reverse order was noted as follows: An organism of the mucosus type was isolated from an exudate. The colonies were green and mucoid and without a hemolytic zone. This organism was injected into the vein of a rabbit and a few days later arthritis appeared in one of the hind legs of the animal. The joint became enlarged and distinct fluctuation was present. After a number of days the joint was aspirated and a small amount of a seropurulent exudate obtained. When plated, this yielded a pure growth of a streptococcus which was strongly hemolytic, and the colonies showed no green color and no marked mucoid or spreading growth.

The transformation of *Streptococcus viridans* into an organism

quite like the pneumococcus and the reverse process have been noted especially by Rosenow¹ in connection with his exhaustive work on the endocarditic cocci. He believes that *Streptococcus viridans* is a modified pneumococcus and by altering certain growth conditions, the one may acquire the properties of the other.

In order further to test the relations of members of the streptococcus group it was thought that possibly anaphylactic reactions which have been applied to other groups of bacteria might be of value here.

Kraus and Doerr² have shown that guinea-pigs sensitized to typhoid bacilli, while reacting to typhoid bacilli, would not react to such closely related organisms as the dysentery bacillus and the paratyphoid bacillus. Also guinea-pigs sensitized to the cholera vibrio would not react to the typhoid bacillus nor to some apparently closely related organisms (*Vibrio Nasik*). They point out that this method may be of value in determining the relationship of bacteria.

Guerrini³ tested various bacterial nucleoproteids and concluded that anaphylaxis is specific for the "Bacterienart" from which the nucleoproteid was obtained. In his experiments he made inter-anaphylactic tests with *B. pestis*, *vib. cholerae*, and certain organ nucleoproteids but did not use proteids from such closely related organisms as did Kraus and Doerr.

Guinea-pigs were sensitized intraperitoneally with small amounts of cocci (one-half slant growths), which had been grown for 24 hours on human blood agar free from water of condensation and then suspended in salt solution. Washing of the bacteria was done in some instances but was found unnecessary. Furthermore Bøehnke and Bierbaum⁴ found that the peptone in the media plays no part in the sensitization with bacteria because the phenomenon is not altered by using peptone free media. This factor therefore could be disregarded. After an interval of from 14 to 26 days they were intoxicated, intracardially or by injections into the jugular vein, with the various organisms to be tested. The growth from two or three large slant tubes was used for intox-

¹ *Jour. Infect. Dis.*, 1910, 7, p. 411.

² *Wien. klin. Wchnschr.*, 1908, 21, p. 1008.

³ *Ztschr. f. Immunitätsf. u. exp. Ther.*, 1912, 14, p. 70.

⁴ *Centralbl. f. Bakteriöl.*, 1 Orig., 1912, 65, p. 504.

ication and for culture media; horse blood agar was used in many instances though the human blood media, such as was used for sensitization, gave apparently the same results. The organisms in all instances were immediately injected after suspension in order to avoid the formation of anaphylatoxins.

The results are given in Table 2. In the first place organisms of the type of *Streptococcus hemolyticus* appear to interact freely. For example, a streptococcus (243) isolated from the tonsils in a case of acute follicular tonsillitis reacted with *Streptococcus hemolyticus* from a case of erysipelas. Streptococci isolated from ordinary sore throats react with cocci from throats of chronic arthritis as do also hemolytic streptococci causing otitis media. Furthermore organisms of the ordinary hemolytic variety react with organisms of the type we have called "epidemicus." In this group may be considered a streptococcus which was isolated from the udder of a cow suffering from mastitis. This organism after animal passage acquired the characteristics of the epidemic streptococcus. It reacted positively with a hemolytic streptococcus isolated from the throat of a case of ordinary tonsillitis. A strain of streptococcus known as the "grip" streptococcus was kindly sent to me by Dr. Seligmann of Berlin. This organism was isolated from a patient suffering from a streptococcus infection which appeared in epidemic form among children, the symptoms of which were a severe "grippe." The epidemic occurred in Rummelsburg, Germany, in 1911, and has been reported in detail by Müller and Seligmann.¹ The streptococcus has the characteristics of *Streptococcus epidemicus* after animal passage, though when first received it resembled more closely *Streptococcus hemolyticus*. Dr. Seligmann² called my attention to the fact that it had lost on artificial media many of its peculiarities. It reacts strongly positive in a guinea-pig sensitized with a typical hemolytic streptococcus (243), exactly as do the epidemic streptococci isolated here in Chicago. A strain of streptococcus, isolated during the milk epidemic in Boston in 1911, obtained from Dr. Fabyan of Boston, reacted with an animal sensitized with a typical hemolytic streptococcus. Also a streptococcus isolated from the Chicago epidemic reacted

¹ *Berl. klin. Wchnschr.*, 1911, 48, p. 1636.

² Personal communication.

TABLE 2.

INTERANAPHYLACTIC REACTIONS IN GUINEA-PIGS WITH STREPTOCOCCI.

	Sensitizing Organism	Intoxicating Organism	Interval between Inoculations	Result
1	Str. hemolyticus (225). Isolated from middle ear discharge.	Str. hemolyticus (225). 2½ slant growths intracardially.	17 days	Death in 4 minutes from typical anaphylactic shock. Lungs very pale and markedly distended.
2	Str. hemolyticus (256). Isolated from tonsillar crypts in a case of chronic arthritis which promptly recovered following extirpation of tonsils.	Str. hemolyticus (225). 2 slants intracardially.	17 days	Death in 3 minutes from violent anaphylactic shock. Lungs show characteristic distention.
3	Str. hemolyticus (256).	Str. hemolyticus (243). From tonsils in a case of follicular tonsillitis. Injected 2 slant growths.	21 days	Typical symptoms of anaphylaxis in 1 minute. Animal dead in 3 minutes. Lungs very emphysematous.
4	Str. hemolyticus (257). Isolated from tonsils in a case of chronic rheumatism.	Str. hemolyticus (256). 3 slants injected.	17 days	In a few minutes slight but definite symptoms of shock. Recovery.
5	Str. hemolyticus (243).	Str. from erysipelas. 3 slant tubes injected into jugular vein.	19 days	In 2 minutes symptoms appeared. Restlessness, defecation, hair raised about head, rubbing of nose, squeals at intervals. No definite spasms. Recovery.
6	Str. hemolyticus (243).	Str. "Madel." Isolated by Dr. Seligmann from case of grip epidemic in children in Germany. 2 slants injected intracardially.	17 days	In about 2 minutes distinct signs of shock. Recovery.
7	Str. "Madel."	Str. "Madel." 2 slant growths intracardially.	17 days	Slight but distinct symptoms of anaphylaxis in few minutes. Recovery.
8	Str. hemolyticus (229). Isolated from ear discharge.	Str. epidemicus (211). Isolated from spleen at autopsy.	22 days	Death in about 3 minutes from typical anaphylactic shock. Lungs very highly distended.
9	Str. hemolyticus (250). Isolated from tonsils in child suffering with slight heart lesion.	Str. epidemicus. Isolated by Dr. Fabyan during Boston epidemic. 4 slant tubes injected.	22 days	In 2 minutes distinct anaphylactic shock. Spasm very marked. Gradual recovery.
10	Str. hemolyticus (243).	Str. mucosus. Isolated from ear discharge. 2 slants injected into heart.	24 days	Immediate convulsions. Respirations very violent. At intervals severe spasms. Gradual improvement. Death after 12 hours. Lungs moderately distended.
11	Str. hemolyticus (243).	Str. pneumoniae. Isolated from pleural cavity at autopsy in case of lobar pneumonia. 3 slant tubes injected into jugular vein.	19 days	In about 4 minutes, spasms, rubbing of nose, heavy breathing, etc. After one hour animal still having spasms. Killed. Lungs very emphysematous. Hemorrhages into stomach and myocardium.
12	Str. hemolyticus (243).	Str. pneumoniae. Isolated from rusty sputum of case of lobar pneumonia. Injected into jugular vein.	26 days	After 3-4 minutes distinct spasms, very restless, heavy breathing, rubbing of face, etc. Gradually recovered. Two days later given Str. hemolyticus. No reaction. Animal killed in 15 minutes. Lungs show no emphysema.

TABLE 2.—Continued.

	Sensitizing Organism	Intoxicating Organism	Interval between Inoculations	Result
13	Str. epidemicus (214).	Str. pneumoniae (same as No. 11).	14 days	In a few minutes animal showed distinct symptoms. Rubbing of nose, defecation, jerky spasms, restlessness, etc. Recovery.
14	Str. pneumoniae. Isolated at autopsy.	Str. hemolyticus (243) into heart.	21 days	After about one minute violent spasms appeared with death in 4 minutes. Lungs highly emphysematous.
15	Str. epidemicus. Isolated from udder of cow suffering from mastitis.	Str. hemolyticus (243). Intracardial injection.	22 days	After a few minutes distinct symptoms. Hair on head erect, frequent defecation, scratching of nose, heavy breathing. Died in 20 minutes from hemorrhage into pericardium. Lungs distinctly emphysematous.
16	Str. epidemicus (strain from Boston epidemic).	Str. epidemicus (233). Isolated during Chicago epidemic.	22 days	In a few minutes signs of anaphylaxis. Restlessness, defecation, jerky spasms, rubbing of nose, etc. Recovery.
17	Str. epidemicus (233).	Str. viridans. Isolated from case of endocarditis.	26 days	No distinct signs of anaphylaxis. Had some circus movements. Died during night. Lungs showed questionable evidence of anaphylaxis.
18	Str. hemolyticus (243).	Str. viridans (endocarditis). 3 slant tubes injected into jugular vein.	19 days	Practically no symptoms. No spasms or restlessness. 5 days later injected intracardially 2 tubes Str. hemolyticus 243. Typical spasms with death after few minutes. Lungs emphysematous.
19	Str. hemolyticus (243).	Str. viridans (endocarditis). Intracardial injection.	24 days	No definite symptoms. Killed after 20 minutes. Lungs practically normal.
20	Str. hemolyticus (243).	Sta. albus. Isolated from skin. 2 slant cultures.	15 days	No symptoms.
21	Str. hemolyticus (243).	Sta. albus. Isolated from furuncle. 2 slant cultures.	15 days	No definite symptoms.
22	Str. hemolyticus (243).	Sta. aureus. Isolated from carbuncle. 2 slant cultures.	15 days	No definite symptoms.
23	Normal guinea-pig.	Injected with 2 tubes of Str. hemolyticus (243).	No anaphylactic symptoms.
24	Normal guinea-pig.	Injected with 2 tubes of Str. epidemicus.	No symptoms.
25	Normal guinea-pig.	Injected with 3 tubes of Str. viridans.	No anaphylactic symptoms.

positively with a guinea-pig sensitized with the Boston streptococcus. Furthermore it was found that a typical *Streptococcus mucosus* reacted very definitely with an animal sensitized with the

hemolytic streptococcus and also with the epidemic streptococcus. Likewise the hemolytic streptococcus reacted in an animal sensitized with *Streptococcus pneumoniae*. Two strains of *Streptococcus pneumoniae* were tested, one of which was isolated from the heart's blood postmortem; the other was isolated in pure culture from the sputum of a case of lobar pneumonia.

Streptococcus viridans in my experiments failed to react with animals sensitized with the hemolytic streptococcus; or at least the reaction, if present at all, was very slight. Furthermore, two days later one of the animals reacted promptly to an intoxicating injection of the sensitizing streptococcus. *Streptococcus viridans* used in these experiments was isolated by blood culture from a case of chronic infective endocarditis.

Animals sensitized with *Streptococcus hemolyticus* were intoxicated with *Staphylococcus albus* from the skin, one from an abscess and a *Staphylococcus aureus* from a carbuncle. No reaction appeared in any instance.

The above results seem to indicate that there is a close relationship between various members of this group with the exception of the organisms of the viridans type. In the interpretation of these results I think caution should be used. It is undoubtedly true that the bacteria mentioned have anaphylactic factors in common, but I would not consider the data as excluding the possibility of the existence of certain specific elements in the various organisms such as Wells[†] has shown to occur in certain closely related vegetable proteins. In order to determine this point, more careful studies, especially with chemically purified bacterial proteins, will have to be made.

The results of the anaphylactic experiments agree in a general way with the data given in the first part of the paper. They tend to corroborate the idea brought out in Table 1 and with possibly one exception explain the apparently easy transition from one member to another. The failure of *Streptococcus viridans* to react was not expected. It may be that there is a gap existing between this organism and the other members of the series which might be bridged over by strains occupying intermediary positions.

[†] H. G. Wells, paper read before the Chicago Path. Soc., February 10, 1913.

I used an endocarditic coccus isolated from the blood in my experiments because this organism seems to be more uniform in its various properties and therefore more representative of this group than organisms isolated from other sources. Cocci of the viridans type from the throat may vary considerably in many ways; for example, in pathogenicity, morphology, character of zone on blood agar, etc. It is possible that we have here to deal with a group of organisms whose limits relatively are very wide and I think many strains of cocci of this type isolated from various sources should be tested by anaphylactic reactions with the view of clearing up this point.

I wish to state that Table 1 is not intended to be a complete classification of streptococci. However, I believe a complete and satisfactory classification must rest upon some such conception as is here brought forth. There are undoubtedly organisms of this group other than those mentioned in this paper which may find a place in the series. I have observed cocci, isolated especially from the throat and from sputum, which are different in certain respects from *Streptococcus viridans*, and yet they would appear to occupy a position in the series either just above or just below this organism. I have also observed a very highly hemolytic streptococcus isolated from an alveolar abscess whose growth is very delicate and dry and which I think might be placed in the series just above *Streptococcus hemolyticus*. Furthermore it may very well be that with further study it will be necessary to alter the relative positions of some of the members in the series as it is given above in Table 1.

SUMMARY.

The data in this paper are arranged in such a way as to indicate a biologic classification of members of the streptococcus group. Hemolysis, growth on blood agar, capsule formation, solubility in bile, sugar reaction, pathogenic properties in animals and anaphylactic reactions are considered. Transformation of one member into another within certain limits appears to be a not uncommon phenomenon.